Heart Failure Association of the European Society of Cardiology Practical Guidance on the Use of Natriuretic Peptide Concentrations

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Abstract

Natriuretic peptide (NP; B-type NP [BNP], N-terminal proBNP [NT-proBNP], and midregional proANP [MR-proANP]) concentrations are quantitative plasma biomarkers of the presence and severity of hemodynamic cardiac stress and heart failure (HF). End-diastolic wall stress, intracardiac filling pressures and intracardiac volumes seem to be the dominant triggers. This paper details the most important indications for NPs and highlights eleven key principles underlying their clinical use shown below.

• NPs should always be used in conjunction with all other clinical information.

• NPs are reasonable surrogates for intracardiac volumes and filling pressures.

• NPs should be measured in all patients presenting with symptoms suggestive of HF such as dyspnea and/or fatigue, as their use facilitates the early diagnosis and risk stratification of HF.

• NPs have very high diagnostic accuracy in discriminating HF from other causes of dyspnea: the higher the NP, the higher the likelihood that dyspnea is caused by HF.

• Optimal NP cut-off concentrations for the diagnosis of acute HF (very high filling pressures) in patients presenting with acute dyspnea to the emergency department are higher as compared to those used in the diagnosis of chronic HF in patients with dyspnea on exertion (mild increase in filling pressures at rest).

• Obese patients have lower NP concentrations, mandating the use of lower cut-off concentrations (about 50% lower).

• In stable HF patients, but also in patients with other cardiac disorders such as myocardial infarction, valvular heart disease, atrial fibrillation, or pulmonary embolism NP concentrations have high prognostic accuracy for death, and HF hospitalisation.

• Screening with NPs for the early detection of relevant cardiac disease including left ventricular systolic dysfunction in patients with cardiovascular risk factors may help identify patients at increased risk therefore allowing targetted preventive measures to prevent HF.• BNP, NT-proBNP, and MR-proANP have comparable diagnostic and prognostic accuracy.

• In patients with shock, NPs cannot be used to identify cause (e.g. cardiogenic versus septic shock), but remain prognostic.

• NPs cannot identify the underlying cause of HF and therefore, if elevated, must always be used in conjunction with cardiac imaging.

1. Introduction

Natriuretic peptides (NP; B-type natriuretic peptide [BNP], N-terminal proBNP [NT-proBNP]) are quantitative plasma biomarkers of the presence and severity of hemodynamic cardiac stress and heart failure (HF). This paper gives their most important indications and highlights key principles underlying their clinical use:

NPs are of substantial medical value for the diagnostic evaluation of suspected HF.[1,2] This indication is supported by several diagnostic and randomised controlled studies and is consistently recommended in clinical practice guidelines.[1,2] NPs also can help in a broad range of other indications, including prognostication of patients with established cardiovascular disorders such as myocardial infarction, valvular heart disease, HF, and pulmonary embolism.[3,4] Overall, BNP and NT-proBNP have comparable diagnostic and prognostic accuracy[5–8]; other natriuretic peptides such as ANP (or MR-proANP) are also comparable, but less well-documented. Accordingly, all recommendations apply to the use of NPs in general. Though of substantial value for serially assessing prognosis in those with HF, randomised controlled intervention trials have provided inconsistent results regarding the medical value of using NP concentrations to guide treatment in patients with HF, rendering this indication controversial.[9–11] The purpose of this review is to provide clinicians with advice on the use of NP concentrations as a diagnostic aid in their daily practice.

The concentrations of the three appropriately validated NPs (BNP, NT-proBNP, MR-proANP) correlate closely with each other. However, their individual values are NOT interchangeable and their normal ranges and optimal cut-off concentrations differ.

Two important principles should underlie the clinical use of NPs. **First**, a NP measurement should never be a stand-alone test. It is always of greatest value when it complements the physician's clinical skills along with other available diagnostic tools. Results should always be interpreted in consideration of renal function, and body mass index (BMI),

the two most powerful confounders of NP concentrations.[12–20] **Second**, NP concentrations should be interpreted and used as continuous variables in order to make full use of the biological information provided by the measurement (similar to calculated glomerular filtration rate). Cut-off concentrations may still be useful to make the application of NP easy for physicians without extensive experience with NP testing.

Table 1. Key principles for the use of NPs in clinical practice.

NPs should always be used in conjunction with all other clinical information.
NPs are reasonable surrogates for intracardiac volumes and filling pressures.
NPs should be measured in all patients presenting with symptoms suggestive of HF such as dyspnea and/or fatigue, as their use facilitates the early diagnosis and risk stratification of HF.
NPs have very high diagnostic accuracy in discriminating HF from other causes of dyspnea: the higher the NP, the higher the likelihood that dyspnea is caused by HF.
Optimal NP cut-off concentrations for the diagnosis of acute HF (very high filling pressures) in patients presenting with acute dyspnea to the emergency department are higher as compared to those used in the diagnosis of chronic HF in patients with dyspnea on exertion (mild increase in filling pressures at rest).
Obese patients have lower NP concentrations, mandating the use of lower cut-off concentrations (about 50% lower).
In stable HF patients, but also in patients with other cardiac disorders such as myocardial infarction, valvular heart disease, atrial fibrillation, or pulmonary embolism NP concentrations have high prognostic accuracy for death, and HF hospitalisation.
Screening with NPs for the early detection of relevant cardiac disease including left ventricular systolic dysfunction in patients with cardiovascular risk factors may help identify patients at increased risk therefore allowing targetted preventive measures to prevent HF.
BNP, NT-proBNP, and MR-proANP have comparable diagnostic and prognostic accuracy.
In patients with shock, NPs cannot be used to identify cause (e.g. cardiogenic versus septic shock), but remain prognostic.

NPs cannot identify the underlying cause of HF and therefore, if elevated, must always be used in conjunction with cardiac imaging.

HF: heart failure; NP: natriuretic peptide.

2. Physiology

Although NP levels can be modulated by lesser understood mechanisms, the most important one is in the setting of volume expansion and/or pressure overload: the resulting end-diastolic wall stress initiates synthesis of NP precursors in the ventricular and atrial myocardium. [12,21–25] Further, BNP/NT-proBNP are exclusively produced by the cardiac tissue, and as such, NPs production reflects wall stress, a product of intracardiac volumes and filling pressures. Through binding to multiple NP receptors, NPs lead to natriuresis, diuresis, vasodilation, improved myocardial relaxation, and reduced myocardial fibrosis.[26] Thus, NPs serve an important regulatory role by opposing the vasoconstriction, sodium retention, and antidiuretic effects of the activated renin–angiotensin–aldosterone (RAS) and sympathetic nervous systems.[27] The biochemistry of NP release and breakdown is complex and is discussed elsewhere.[28–32]

Figure 1 illustrates the haemodynamic determinants of NPs.

A given NP concentration is a summation of many inputs and is a measure of many aspects of cardiac function. It is critically important to remember both BNP and NT-proBNP are not solely biomarkers of left ventricular (LV) systolic function; indeed, a broad range of structural and functional cardiac abnormalities may lead to meaningful elevation of NPs, including LV diastolic dysfunction, right ventricular dysfunction, valvular dysfunction, increased pulmonary pressures, and atrial arrhythmias.[12,23,33–35]

3. Diagnosis of HF

The unmet clinical need: HF, a progressive disease with a mortality exceeding most cancers, presents a major burden to health care systems.[36] Most patients with HF eventually present to the emergency department (ED) or hospital typically due to symptoms related to congestion. Because HF occurs predominantly in older subjects, its presentation is often complicated by multiple co-morbidities. This is unfortunate, since the most common presentation of HF is dyspnoea, a complaint that is neither specific nor sensitive for predicting the presence of HF. Additionally, though physical findings in HF such as bilateral basal pulmonary end-inspiratory rales, elevated jugular venous pressure, and leg oedema are relatively specific for the diagnosis, their sensitivity is limited (only 50-60%). Similar limitations apply to the ECG and chest x-ray. Accordingly, diagnostic uncertainty frequently remains high after clinical assessment.[37–40] In the *Breathing Not Properly* study, at an 80% cut-off level of certainty of HF, clinical judgment had a sensitivity of only 49%.[37]

The evidence: Diagnostic studies comparing measurements of NPs against a reference standard diagnosis of HF (or alternative diagnosis) have consistently shown that NPs have very high diagnostic accuracy for HF.[16,41,42] Moreover, NPs improve the diagnostic accuracy of clinical judgment in the ED. This observation is also true for adults >75 years old despite the slightly diminished diagnostic accuracy for NT-proBNP in this age group.[16] In addition, three randomised controlled trials have showed that earlier and more accurate diagnosis of HF translates into medical and economic value for patients, physicians, and the health care system.[38,43,44]

Recommendation: NP should be measured in all patients presenting with symptoms suggestive of new-onset or worsening of HF such as dyspnea and/or fatigue, as their use facilitates both the early diagnosis or the early exclusion of HF.

Practical guidance: As a quantitative marker of HF, NP concentrations are best interpreted as a continuous variable: very low NP concentrations have a very high negative predictive value (NPV) to exclude the presence of HF. On the other hand, the higher the NP concentration, the higher the likelihood that dyspnea is due to HF.[38,39,45,46] Also, optimal NP cut-off concentrations for the diagnosis of acute HF (very high filling pressures) in patients presenting with acute dyspnea to the ED are higher as compared to those used in the diagnosis of chronic HF in patients with dyspnea on exertion (mild increase in filling pressures at rest, Table 2). Combined with echocardiography in patients with elevated NPs, NP-testing enables the rapid and accurate diagnosis of HF, and its phenotypes (Figure 2).[47] Given elevation of NPs occurs in critically ill patients such as shock (including that caused by sepsis), elevated concentrations are not specific for cardiogenic causes of shock; other diagnostic approaches including immediate echocardiography need to be used. However, elevated NP concentrations in shock of any cause are prognostic.[48,49] In patients with an established diagnosis of HF, the measurement of NPs is not nessessery at all follow-up visits but whenever it is unclear whether and to what extent the reported symptoms are related to HF.

Figure 2. Diagnostic algorithm for HF.

In patients with suspected acute HF, a BNP cut-off concentration of 100 pg/mL provides an excellent NPV to exclude the presence of HF, while higher values >400 pg/mL deliver excellent positive predictive value (PPV).[39] As NT-proBNP shows a stronger correlation with age and renal dysfunction, age-dependent rule-in cut-offs are preferred for NT-proBNP (450/900/1800 pg/mL),[41] while independent of age a NT-proBNP <300 pg/mL provides a very high NPV for HF. These results were recently affirmed.[16,17]

Considering "rule-in" thresholds requires addressing the fact that NPs may be persistently elevated in chronic HF and may not be representative of an acute haemodynamic

change. Knowledge of each patient's individual NP concentration when stable (the so-called "dry" NP concentration) helps to interpret concentrations of these markers when such patients present with acute symptoms; a change of 100% or more from the stable concentration suggests a change in clinical state, such as decompensation.[50,51]

When confronted with an elevated NP, other conditions that result in an increased concentration of these peptides should also be considered, including both those that result in myocardial end-diastolic wall stress (acute pulmonary embolus, acute coronary syndrome, primary pulmonary hypertension, etc.) and renal failure, and therefore also represent HF per se.[52]

3.1 Caveats in using NP levels

3.1.1 "Grey zone"

The "grey zone" is defined in Table 2.

Table 2. Recommended NPs` cut-offs for the acute HF diagnosis* [1,12,16,39]

	Cut-off levels (pg/mL)					
	NT-proBNP			**BNP**		
	Age <50	Age 50-75	Age >75	Age <50	Age 50-75	Age >75
Acute setting, patient with acute dyspnea						
HF unlikely	<300			<100		
„Grey zone"	300–450	300–900	300–1800	100–400		
HF likely	>450	>900	>1800	>400		
Non-acute setting, patient with mild symptoms						
HF unlikely	<125			<35		
„Grey zone"	125-600			35-150		
HF likely	>600			>150		

HF: heart failure; BNP: B-type natriuretic peptide; NT-proBNP: amino-terminal BNP
*consider reducing the cut-off levels in obese patients by 50%.

The grey zone needs extra physician attention and ancillary testing. While the final

diagnosis is often mild to moderate HF,[39,53–55], or HFpEF rather than HFrEF, other causes of a modest rise in NP level should be considered. In acute dyspnoea, "grey zone" NP values are present in 20% of patients and about 50% of these will have acute HF. Other causes include primary non-cardiac pathology that causes myocardial stress, and includes pulmonary hypertension and RV dysfunction secondary to pulmonary embolism, pneumonia, and cor pulmonale.[56–58]

The grey zone levels are far more strongly associated with HF when concomitant clinical features are present, such as a history of heart failure, jugular venous pressure, and prior diuretic use.[55]

3.1.2 Pulmonary disease

In patients with chronic pulmonary disease, differentiating between pulmonary causes of dyspnoea versus confounding cardiac disease can be clinically challenging. Importantly, previously unsuspected, "masked", HF may be present in those with COPD. In this context, elevation of NPs may be useful to identify presence of unrecognized HF however it is necessary to remember in patients with pulmonary hypertension and RV dysfunction (e.g. in severe COPD), NP levels are often in the grey zone and occasionally in the diagnostic zone for HF, reflecting the existence of major RV stress and, in effect, right HF.[56,57,59–63] The accuracy of NP to diagnose HF is unchanged in the presence of pre-existing pulmonary disease.[58,62,63]

3.1.3 Renal disease

There is an important interrelationship between cardiac and renal dysfunction. About one third of outpatients with chronic HF have renal dysfunction.[64] Current data suggest that the cause of elevated NP concentrations in renal dysfunction is multifactorial, representing in part a true counter-regulatory response from the heart to the kidney, and not only diminished passive renal clearance.[15,46] It is a major misconception that NPs are solely removed from circulation by the kidneys; indeed only 25% of clearance of NPs is related to renal filtration,[20] with the balance

of their clearance due to removal by various organs with high blood flow.[65] In order to maintain optimal diagnostic performance, the cut-off concentrations for detecting HF may need to be raised when estimated glomerular filtration rate (eGFR) is less than 60 ml/min.[46] Due to the strong correlation between renal dysfunction and age, no additional adjustment seems nessessary for NT-proBNP once using age adjusted rule-in cut-offs. For BNP, the impact of renal dysfunction overall is smaller, and increasing the rule-out ut-off tp 200 pg/ml rather than 100 pg/ml seems sufficient.[46] Overall, it is imiportant to highlight that renal dysfunction and its associated cardiac comorbidities, and not age per se, seem to be the major driver behind the higher NT-proBNP and BNP concentrations in elderly patients.[14] Due to incomplete data, NP testing for HF should be discouraged in patients on dialysis. Importantly, high NP concentrations should not be ignored in the setting of renal dysfunction.[66] Given the strong relationship between cardiac and renal disease, clearly elevated NP concentrations suggest that cardiac disease is present and should influence clinical decision-making.

3.1.4 Diastolic dysfunction

In accord with the cardinal role of myocyte stretch in generating NP synthesis and release, the severity of diastolic dysfunction is correlated to increased plasma concentrations of both BNP and NT-proBNP.[67,68]

3.1.5 Atrial arrhythmia

It is well-established that the presence of atrial arrhythmias such as atrial fibrillation or flutter are associated with higher concentrations of NPs.[69] On occasion, the values of these peptides may be in excess of the threshold for "HF", even in the absence of further clinical support for the diagnosis.[70] In those presenting with recent onset dyspnoea and concurrent atrial fibrillation, HF is present in at least 65 % of cases. From a pathophysiological and clinical perspective, these patients should be considered to have HF until proven otherwise. Subclinical myocardial stress must be assumed in such patients regardless of results from echocardiography. In addition,

the onset of atrial arrhythmia is a common cause of decompensated HF, and in the presence of such an arrhythmia, HF is often more severe and associated with a worse prognosis.[71] An even more elevated plasma level of BNP or NT-proBNP in those with atrial fibrillation or flutter is speculated to be due to release of peptide produced in the atria, however increased ventricular myocardium release, owing to higher wall stress from tachycardia, is also possible.[72]

3.1.6 Patients treated with sacubitril/valsartan

Sacubitril/valsartan seems to affect the concentration of NPs that are cleared by neprilysin such as BNP and ANP also by its direct pharmacologic effect on neprilysin (inhibition) and not only by its effect on intracardiac filling pressures.[73–75] While the mechanisms underlying the effect of sacubitril/valsartan on NP concentrations and NP activity are a matter of ongoing research,[76,77] at this point in time we consider NT-proBNP the preferred biomarker to quantify HF severity and monitor prognosis in patients on sacubitril/valsartan.[33]

3.1.7 Patients with acute and chronic ischemia

Natriuretic peptides independently and accurately predict mortality in patients with acute coronary syndrome (ACS), but do not seem to provide added diagnostic information.[78–80] Similarly, natriuretic peptides do not further increase diagnostic accuracy on top of clinical judgment and/or troponin measurements in the detection of inducible myocardial ischemia.[81,82] It is currently unclear how the pathophysiological signals quantified by the elevation of natriuretic peptides in ACS patients could be best used clinically, in order to mitigate the identified high mortality risk.[78,83]

3.2 Caveats: lower than expected concentration of natriuretic peptides

3.2.1 Obesity

Concentrations of both BNP, NT-proBNP, and MR-proANP are lower in obese persons, both with and without HF.[84–87] Although the reason for this interaction remains incompletely understood (possibly including pericardial fat),[86,88] given different mechanisms of clearance for

BNP, NT-proBNP and MR-proANP, this finding is most likely due to lower release of NPs in obesity, rather than increase in their clearance. Furthermore, with substantial weight loss, rise in NP concentrations are seen, implying a ‚de-repression' of their lower values.[89] Mechanistically, this may be due to suppression of the *bnp* gene by circulating factors such as androgens that may be produced by adipose tissue.[90] It is noteworthy a unique relationship exists between BNP and adipose tissue: increased concentrations of NP receptors are found on adipocytes, and BNP induces lipolysis. This has led some to postulate that increased clearance might add to lower BNP levels in obesity,[91,92] but given absence of clearance of NT-proBNP by NP receptors, this cannot entirely explain the inverse association between body-mass index (BMI) and NP concentrations. Clinically, caregivers should recognize risk for lower NP concentrations in those with BMI ≥30 kg/m^2; such values are typically not "normal", and more often closer to diagnostic thresholds than not. To optimize diagnostic accuracy**, lowering of established cut-off concentrations by up to 50%** in obese patients is reasonable.[18] As there is a linear decrease in NP levels with increasing BMI, the higher the BMI the lower the cut-off concentration which provides the highest accuracy.[18,67] A very low BNP cut-off concentration (<50 pg/mL) should be used to rule-out HF in obese patients. Neglecting this concept would invariably result in suboptimal sensitivity.[93] Recently, it was demonstrated that the differenbces ascribed to obesity are in part explained by sex differences: men have lower NP levels than women, but weigh much more.[78] Given the large overlap between obesity and HFpEF, and the generally lower levels of NP even in non-obese HFpEF, this aspect is particularly important for the diagnosis of HFpEF.[93–95] Despite the lower circulating levels, NP levels retain prognostic performance in obese as well as HFpEF patients.[18,67,96,97]

3.2.2 HF due to causes upstream from the LV

When HF is due to a cause upstream from the LV, for example in mitral stenosis or acute mitral regurgitation, NP concentrations may be initially low despite severe symptoms. The absence of

a significant rise in LV wall stress in these acute settings explains the lack of marked NP production, and while NP levels may still be higher than normal, they will not rise to the same degree as when the HF occurs with a concomitant overload on the LV. Similarly, pericardial abnormalities, such as constriction and tamponade, can sometimes cause symptoms of HF; however, since the myocardial wall is not abnormally stressed, NP levels are typically normal or only slightly elevated.[98,99] Early echocardiography is mandatory whenever suspecting HF due to a cause upside the LV such as mitral stenosis as well as in suspected pericardial tamponade.

3.2.3 Flash pulmonary oedema

NP levels may be relatively low in patients presenting with HF symptoms that develop abruptly, e.g. within one hour. In this setting, the time interval between the initial trigger and the measurement of NP levels is so short that it precedes the up-regulated peptide synthesis. Since only very small quantities of BNP (compared to atrial natriuretic peptide) are stored in secretory granules, the development of elevated BNP concentrations in “flash” pulmonary oedema is dependent upon the de novo synthesis and secretion of the peptide.[100] The incidence of this phenomenon seems to be very low, given underlying sub-critical congestion in those who subsequently develop “flash” pulmonary edema.[38,39,101,102]

3.2.4 Fatigue

In some patients with HF, fatigue is the dominant symptom, while dyspnea is mild or even absent. The diagnostic performance of NP and the optimal cut-off concentrations of NPs in this setting are less well established as compared to patients with dyspnea as the key symptom.[1,2]

3.3 Natriuretic use in the community: linking primary and secondary care

Background: While first coming to prominence in the acute setting, it is in the community that NP may have its widest application. Presently, there are three clinical settings where one should consider using NPs with varying levels of proof or guideline support.

3.3.1 Established role: diagnosing HF

Diagnosing new-onset HF in the community can be challenging. Suggestive symptoms are common, but often non-specific and physical signs often unremarkable. It is here that NP can be very helpful to the physician. Much as in the ED setting, evaluation of dyspnea often is challenging, with numerous diagnostic possibilities. Accordingly, use of NPs to clarify diagnostic evaluation in less acute settings has the same rationale. Although the number of studies in primary care is smaller as compared to those performed in the ED, most of the concepts and findings already discussed regarding use of NPs for diagnostic evaluation of HF in the ED also apply in outpatient testing, including the importance of cardiac and non-cardiac variables influencing concentrations of these peptides. Nonetheless, current evidence strongly supports the use of NP testing also in primary care for the correct evaluation of HF.[103–107]

NP-testing in primary care is widely available both point-of-care, as well as using locally established sample pathways to central laboratories. It empowers the position of the GP and provides important guidance for linking primary and secondary care.

In general, owing to their lower concentrations in the primary care setting, the main application of NPs for outpatient use has focused on their sensitivity and NPV; lower concentrations (e.g. BNP <35 pg/mL; NT-proBNP <125 pg/mL; MR-proANP <85 pmol/L) exclude HF with high confidence, whilst higher concentrations require further evaluation.[108] A normal value has an excellent NPV and while an abnormal value does not confirm the diagnosis of HF, it does underline the need for further diagnostic tests, in particular Doppler-echocardiography. Cut-off concentrations used to rule-out HF vary somewhat, dependent on an

agreed strategy of focusing on a strong rule-out test or a value that minimizes false positive results. At present the ESC guidelines recommend a cut-off concentration of 35 and 125 pg/ml for BNP and NT-proBNP respectively, a strategy that favours minimizing false negative results. For NT-proBNP, a stratified approach of 50/75/250 pg/mL for ages <50/50-75/>75 years may be considered as an alternative.[1,109]

3.3.2 Emerging role: NP-screening to prevent HF

Rational: HF prevention will play an increasingly important role in our strategies for the management of this syndrome. A significant challenge in this effort will be the requirement to individualise risk beyond the presence of accepted risk factors. NPs have been shown to be a strong independent indicator of new onset HF and other CV disease.[110] Thus, beside their diagnostic value, low NP concentrations provide useful reassurance to the clinician regarding lower potential cardiovascular risk; this, in turn may be useful for triage decision making.

The success of a population-based screening programme for a disease condition is dependent on disease prevalence, the availability of a screening test that is acceptable, safe and inexpensive, the presence of effective treatment for detected disease, as well as the existence of, and compliance with, a follow-up care system for people at risk or with positive tests.[111] NPs are attractive candidates for screening the general population for subclinical disease for several reasons. **First**, LV dysfunction and the other cardiovascular diseases that are detectable by elevated NP levels are common and cause significant morbidity and mortality.[112] **Second**, NP levels may be elevated early in the disease process, allowing for timely detection of disease prior to symptom onset.[113] **Third**, early treatment of latent disease with medications such as angiotensin converting enzyme inhibitors improves outcomes by preventing the development of symptomatic HFrEF.[114] Notably, natriuretic peptides have limited accuracy in the screening for mildly reduced LV ejection fraction in asymptomatic patients.[115] Finally, several studies have shown that, in the right setting, screening with NPs may prove cost-effective.[116–118]

Evidence: randomized controlled intervention studies

Recently, the *St. Vincent's Screening To Prevent Heart Failure Study* (STOP-HF) project demonstrated that NP-defined risk and intervention reduced new onset HF, asymptomatic LV dysfunction and overall MACE among participants with cardiovascular risk factors (mean age 65 years) recruited from 39 primary care practices.[113] Intervention-group participants with BNP levels of 50 pg/mL or higher underwent echocardiography and collaborative care between their primary care physician and specialist cardiovascular service. A total of 263 patients (41.6%) in the intervention group had at least 1 BNP reading of 50 pg/mL or higher. The intervention group underwent more cardiovascular investigations and received more renin-angiotensin-aldosterone system-based therapy at follow-up (control, 49.6%; intervention, 56.5%; P=0.01). The primary end point of LV dysfunction with or without HF was met in 59 (8.7%) of 677 in the control group and 37 (5.3%) of 697 in the intervention group (odds ratio [OR], 0.55; 95% CI, 0.37-0.82; P=0.003). The incidence rates of emergency hospitalization for major cardiovascular events were 40.4 per 1000 patient-years in the control group vs 22.3 per 1000 patient-years in the intervention group (incidence rate ratio, 0.60; 95% CI, 0.45-0.81; P = .002).[113]

These results were further strengthened by the *NT-proBNP Guided Primary Prevention of CV Events in Diabetic Patients* (PONTIAC) trial in 300 patients with type 2 diabetes (mean age 68 years), elevated NT-proBNP (>125 pg/mL) but free of cardiac disease.[119] The "control" group was cared for at 4 diabetes care units; patients randomized to the "intensified" group were additionally treated at a cardiac outpatient clinic for the up-titration of renin-angiotensin system (RAS) antagonists and beta blockers. The primary endpoint, hospitalization/death due to cardiac disease after 2 years, was significantly reduced in the intensified group.

Evidence: diagnostic studies using echocardiography as the reference

Many people with substantial LV dysfunction do not have typical symptoms, but might be

identified by a simple screening test such as BNP/NT-proBNP.[120] Although echocardiography is the current gold standard for detection of LV systolic dysfunction and many other structural cardiac abnormalities, its cost, limited availability, and complexity in assessing LV diastolic dysfunction make it an impractical choice for population screening. Several investigations have evaluated the use of NP concentrations to identify asymptomatic subjects with reduced LV ejection fraction,[115,121,122] or for a broader range of sub-clinical cardiovascular disorders.[116] Thus, some of these findings demonstrate suboptimal accuracy of NPs as a screening test for LV systolic dysfunction in community cohorts.[115] In the STOP-HF trial, about 3 patients with cardiovascular risk factors had to be screened to detect one patient with BNP concentration > 50 pg/ml, which triggered cardiac work-up.[113] Overall, applying BNP screening using this specific cut-off in the STOP-HF population resulted in a very favourable cost-effectiveness with €1,104 per quality-adjusted life year gain as cardiovascular hospitalization savings offset increased outpatient and primary care costs.[123]

Recommendation: NP measurement by GPs and diabetologists in high risk populations such as those with hypertension or diabetes mellitus helps targeted initiation of preventive measures including medicine up-titration of RAS antagonists and thereby prevent or slow the development of HF.

Figure 3. NP-screening in patients at high cardiovascular risk by GPs and diabetologists is an integral component of integrated patient care pathways aiming to prevent and/or early detect cardiovascular disease including heart failure (HF).

3.3.3 Additional role: assessing new symptoms in HF

NP assessment can be a very useful investigation in the community when assessing clinical deterioration in patients with established HF. These clinical settings can be challenging especially since features can be non-specific and potentially explained by co-morbidities. In

these circumstances, a significant increase in NP above a stable baseline value would support HF as the cause of deterioration, with no significant change from the stable value having the opposite, but equally-important implication. For this to be applied effectively values for NP reflecting the clinically stable state need to be available in the patients record for comparison and would need to be updated regularly.[124,125]

3.3.4 Challenges to use of NP in the community

The major challenge will be knowledge transfer to end-users, to ensure that the nuances of NP interpretation and the influence of multiple confounders are understood. While a very useful biomarker, NP results may be open to misinterpretation, thus potentially leading to incorrect decision-making. As in all other settings, frequent modifiers of NP include atrial fibrillation, renal failure, sepsis, and obesity. Above all else an understanding that a biochemical change value of at least 50% is required for acceptance that the change is likely of clinical relevance.

4. Monitoring prognosis during HF therapy

4.1 Predischarge during hospitalisation for acute HF

Rationale: With current management, patients hospitalised for AHF continue to have unacceptably high rates of mortality and morbidity.[1,2,12,126,127] Patients who are admitted to the hospital with acute HF usually respond symptomatically to treatment, but clinical assessment is unable to assess whether the optimal filling pressures have been achieved. Multiple studies have shown that many patients are discharged while still congested and the extent of remaining congestion is associated with mortality and the risk for another HF hospitalisation.[128,129] The fact that NPs have a short half-life, are easily measured, and provide a quantitative marker of HF severity and prognosis, suggests that they might be a useful guide to judging the success of therapy in acute HF. The goals of using BNP or NT-proBNP is to determine whether a patient

has received adequate decongestive therapy and if their risk for rehospitalisation has been reduced as much as is feasible during their acute treatment.

NP concentrations after treatment have prognostic significance: those with lower values at the time of discharge (or achieving greater relative reduction) have substantially better prognosis than those who are released from acute care with higher concentrations.[130,131] Discharge NP concentrations seem to be the best predictor of 1-year death or rehospitalisation among patients with acute HF, superior to admission values or the change in levels from admission to discharge.[131,132]

Although there are few data defining why NP levels do not decline in some patients despite treatment, several clinical scenarios should be considered. **First** and most importantly, a persistently elevated NP concentration in a stably diuresed patient may actually be the patient's optivolaemic (dry) NP level at this time point due to persistent increased ventricular wall stress necessary to maintain adequate cardiac output. This identifies a treatment-resistant, high risk patient with a poor prognosis. **Another possible scenario** is that a patient with concomitant right-sided HF and significant ascites and/or oedema might diurese many litres further before NP levels actually drop. This is likely due to mobilization of third-space fluid rather than lowering of cardiac filling pressures. Continuing diuresis and/or vasodilatation should eventually lower “wet” NP levels. **Finally**, in some cases treatment simply does not effectively correct central cardiac haemodynamic abnormalities and therefore does not improve cardiomyocyte stress and one should not expect, therefore, to see a decline in this setting; again, this is a high risk patient.

It remains as yet unclear if changing therapy based on measured predischarge NP concentration can reduce rehospitalisation or avert death.[9,133] A recent modest size randomised controlled pilot study was unable to document medical benefit, however in both study arms, those with a substantial reduction in NT-proBNP had superior outcomes to “non-responders”. Common sense would thus dictate for such higher risk patients that do not exhibit responsive

NP concentrations after treatment that more aggressive monitoring and therapy may be wise. Pre-discharge NP levels appear to be more cost-effective than comprehensive Doppler-echocardiographic examination for the prediction of future cardiac death or HF re-hospitalisation.[134] It is reasonable to measure NP levels routinely prior to discharge when optivolaemic status seems to have been achieved by clinical assessment. This also sets a baseline for continued monitoring in the outpatient setting, where NP measurement may be continued. It further allows for individualising decision making regarding timing, frequency and intensity of follow up; those patients with a significant reduction in NP concentration after acute HF treatment are likely to have a benign early post-discharge course, whereas those with higher or non-falling concentrations may merit close follow up, including potential monitoring in the home.[135] However, this indication is still controversial as a small small prospective randomized trial showed neutral results.[10]

4.2 During outpatient visits for chronic HF

Rationale: The concept of serial measurement of NPs as a quantitative measure of HF severity during outpatient visits for chronic HF mirrors the serial measurement of other key biomarkers in other settings such as e.g. eGFR in patients with kidney disorders, arterial blood pressure in arterial hypertension, and blood glucose and HbA1c in diabetes mellitus. Accordingly, serial measurements of NP would allow physicians to empower, educate and motivate HF patients, similar to the use of other disease surrogates in chronic disease such as home blood pressure, blood glucose, and HbA1c. Serial measurement of NPs provides useful and incrementally powerful prognostic information when measured in patients with chronic HF, not only in the setting of HFrEF but also in HFmrEF and HFpEF.[73,96,97,136,137] Changes in NPs over time in patients with chronic HF not only prognosticate risk for adverse outcomes such as hospitalisation or death, but also predicts changes in LV size and function.[137,138]

Though useful, several caveats exist regarding the interpretation of NP concentrations

in outpatient risk monitoring. When a change in a NP concentration is not accompanied by a change in clinical status, this might reflect biological variability or a change in cardiac or renal function that has not yet resulted in symptoms or signs. As a result of both analytical and biological variabilities (haemodynamic, renal, etc.), reference change values (RCV) have been reported to be relatively large for NPs, up to a doubling of results for each biomarker.[139–141] Only one study investigated both chronic HF patients and normal subjets. The other studies only studied normal subjects, where very low NP concentrations were expected and small changes were very likely to be within the domain of biological and/or analytical variation. Any discussion of biological variation in HF is immediately undermined by the fact that present pathological changes determining NP concentration might be challenging to non-invasively measure, such as filling pressures. Accordingly, a more accurate question to ask is: "How much change in NPs must occur to identify presence of change in filling pressures?“ In this regard, among HF patients, a change of 50% seems to indicate a shift in filling pressure.[23] Furthermore, it has been demonstrated that even a considerably small change in weight can trigger a substantial NP alteration.[125]

The combination of symptoms, weight gain, and NP concentration may be the best way to diagnose early decompensation. As for inpatients, proper adjustment of HF management requires NP to be measured together with renal function.

Therapies for HF, such as angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB), mineralocorticoid receptor antagonists (MRA), beta blockers, diuretics, cardiac resynchronization therapy (CRT), and exercise all tend to chronically reduce concentration of NPs in parallel with their benefits; the sole exceptions to this rule include the effect of sacubitril/valsartan on BNP metabolism, where therapy tends to modestly raise concentration of the NP and the early NP raising effect of non-vasodilating beta blockers during their introduction and early titration.[142]

The relationship between therapies for HF, drop in the NP concentrations and the

improvement in patient's symptoms, improved LV function, and subsequent outcome has led to the hypothesis NP-guided treatment might assist in adjusting chronic HF therapy. Despite the neutral results of the *Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in HF* (GUIDE-IT) trial, a recent meta-analysis of all published RCTs to date is suggestive of benefit of a NP guided treatment adjustment approach for all-cause mortality in HFrEF patients (Figure 4).[10,11,143]

Figure 4. All-cause mortality comparison of NT-proBNP–guided versus standard therapy in chronic HFrEF.

In general, it is necessary to recognize the efficacy of any guide to therapy will be most realized in patients that are not receiving adequate, guideline-compliant medical therapy. In other words, those patients managed with aggressive application of therapies for HF might not realise as much benefit from NP measurement to "guide" their care although NP concentrations maintain their prognostic meaning in such patients.

Current understanding of NP-guided HF care suggests the benefit of the approach is most obvious when: 1) a low target NP concentration is attempted (BNP <100 pg/mL; NT-proBNP <1000 pg/mL), 2) therapies must be adjusted to achieve these goals (i.e. if an elevated NP concentration is ignored, the concept of "guiding therapy" is more likely to fail), and 3) a change in therapy would not have otherwise been made if NP measurement had not been performed. Studies that have these characteristics suggest the approach might improve outcome compared to usual care. On the other hand, in studies with very aggressively applied usual care, the approach of NP guidance might not be as likely to further improve outcomes.[10,144,145]

Since the first randomised pilot study of 69 patients with HF and systolic LV dysfunction showing that therapy guided by NP levels reduced total cardiovascular events and delayed time to first event other trials have provided useful insights regarding the approach, and pooled analyses suggest benefit toward reduction in mortality even considering recent neutral trials.[10,11,144,146]

In the *Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure* (TIME-CHF) trial of elderly patients,[147] NP guided HF therapy did not significantly reduce the primary endpoint of 18-month survival free of all-cause hospitalisations (HR=0.91; P=0.39), however survival free of HF hospitalisation was reduced (HR=0.68; P=0.01), particularly in patients aged <75 years (interaction P <0.02). This finding has led to recognition of the importance of comorbidities on ability to achieve optimal medication titration (and thus, reduction in NT-proBNP or BNP); as older patients are more likely to have more complex medical conditions limiting application of guideline-directed medical therapies for HF, it is hardly surprising such patients are less likely to respond to NP guided HF care.[148,149] The *ProBNP Outpatient Tailored Chronic HF Therapy* (PROTECT) trial provided useful pilot data regarding value of NT-proBNP guided HF care.[150] In this study of 151 patients with HF and reduced ejection fraction, NT-proBNP guided care with a goal value of <1000 pg/mL reduced total cardiovascular events compared with usual care (58 events vs. 100 events, p=0.009; logistic odds for events 0.44, p=0.02).

Most recently, the GUIDE-IT study, reported neutral results regarding NT-proBNP guided care.[10] This trial was the largest randomized study to date, examining 894 subjects with HF with reduced ejection fraction treated with either a goal NT-proBNP <1000 pg/mL versus usual care. After a median 15 months of follow up, no benefit of NT-proBNP guidance versus usual care was seen (HR 0.98; P = 0.88). Furthermore, this strategy of NT-proBNP-guided HF therapy had higher total costs and was not more effective than usual care in improving quality of life outcomes.[151] Notably, those patients in the usual care arm were seen an average of 10 visits during follow up, had similar medication doses administered compared to the NT-proBNP arm, and achieved greater reduction in NT-proBNP concentrations when compared to other trials in this topic; this has led some to speculate more than standard intensity treatment was delivered to those in the usual care arm and conversely that therapy in the marker-guided arm of GUIDE-IT was not as aggressive as the trial protocol would appear to dictate.[152,153]

Accordingly, in populations of patients with lesser aggressive application of standard HF medication, it would still seem likely that NP measurements facilitate HF care.

In addition, as outlined in 3.3.4, it is important to highlight that nearly all HF patients report symptoms possibly related to HF during their follow-up visits. NPs are of enormous help to evaluate whether these symptoms are related to HF and increased intracardiac filling pressures. This assessment has direct therapeutic consequences and will usually lead to adjustments of HF medication in case of HF-related symptoms. If NPs concentrations and therefore filling pressures are in the normal range or only mildly elevated (e.g. BNP below 100 pg/ml or NT-proBNP below 400 pg/ml), symptoms most often do have other causes and patients can be reassured that they are not related to HF, and measures directed against the more likely cause can be taken.

5. Risk stratification of pulmonary embolism and pneumonia

The hemodynamic cardiac stress of the left and right heart combined as quantified by NP concentrations has been shown to be a powerful predictor of death in both patients with pulmonary embolism and patients with pneumonia. As a single marker, NPs achieve similar prognostic accuracy as compared to complex multivariable risk scores. [154,155] Measuring NPs may therefore help in the appropriate triage, early admission to an intensive care unit, if at high risk of death, and possibly outpatient management, if at very low risk or death. ESC guidelines state that NPs should be considered in patients with pulmonary embolism.[156] While the use in pneumonia has not been evaluated in other guidelines, we think that the use of NPs in this indication might allow the early detection of previously undiagnosed or underestimated cardiac disease possibly amendable to therapeutic interventions in a relevant proportion of patients with pneumonia and thereby hopefully ameliorate the substantial mortality observed in pneumonia and substantially elevated NPs.[155,157–164] By contrast, low NPs can rule out any relevant cardiac

dysfunction. The clinical relevance of NPs in patients with pneumonia and the proper timing of their measurement should be addressed in future research.

6. Preoperative risk stratification in non-cardiac surgery

In patients undergoing non-cardiac surgery, judging the risk-benefit ratio of the operation including post-operative complications is challenging for both the physician as well as the patient. In this regard, concentrations of BNP and NT-proBNP sampled prior to such surgeries have been shown to be powerful predictors of post-procedural complications, including death, myocardial infarction, and acute HF to allow better informed decisions.[165–167]

Accordingly, current Canadian clinical practice guidelines recommend the measurement of NPs in patients who are 65 years of age or older, are 45-64 years of age with significant cardiovascular disease for preoperative risk stratification.[165] ESC guidelines state that NPs may be considered in this indication.[168]

7. Other evolving indications

Promising other evolving indications include patients with primary pulmonary hypertension, patients with congenital heart disease, patients with valvular heart disease, and critically ill patients in the intensive care unit.[169–177]

8. Conclusion

NPs are the gold standard biomarkers for HF diagnosis and prognosis. The measurement of NPs can help clinicians manage patients in several clinical scenarios. They are helpful in screening to identify or exclude cardiac disease, for the differential diagnosis of symptoms

that might be due to HF and are robust powerful prognostic tools. Each NP has specific cut-off concentrations. Plasma concentrations should be interpreted in the context of the clinical setting and as a quantitative marker of HF. The incremental value of NP-guided therapy remains controversial.

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Figure legends

Figure 1 illustrates the haemodynamic determinants of NPs.

ANP: atrial natriuretic peptide; BNP: B-type natriuretic peptide; NT-proBNP : N-terminal proBNP; NP: Natriuretic peptide; LV: left ventricular; RV: right ventricular; HF: heart failure.

Figure 2. Diagnostic algorithm for HF.

NP: Natriuretic peptide; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; HFmrEF: heart failure with mid-range ejection fraction; LVEF: left ventricular ejection fraction; RV: right ventricular; HF: heart failure.

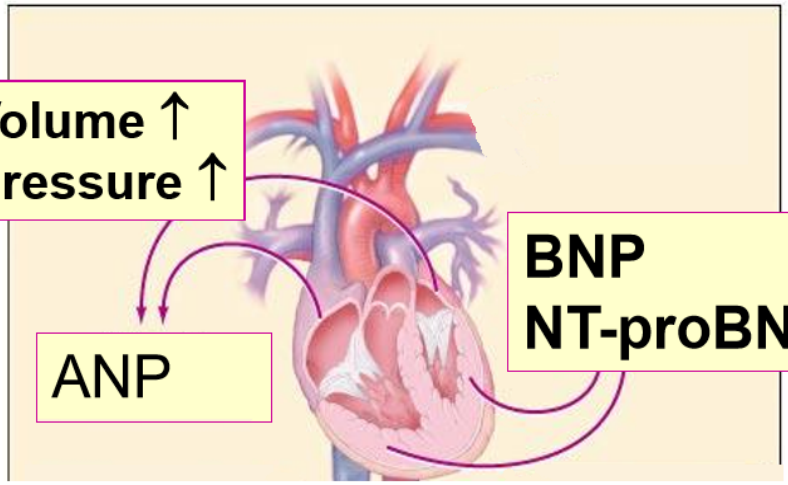
Figure 3. NP-screening in patients at high cardiovascular risk by GPs and diabetologists is an integral component of integrated patient care pathways aiming to prevent and/or early detect cardiovascular disease including heart failure (HF).

NP: Natriuretic peptide; GP: general practitioner; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; LVEF: left ventricular ejection fraction; RV-HF: right ventricular heart failure; VHD: valvular heart disease.

Figure 4. All-cause mortality comparison of NT-proBNP–guided versus standard therapy in chronic HFrEF.

(A) Forest analysis is shown for all-cause mortality in NT-proBNP–guided versus standard therapy. (B) Sensitivity analyses were used to assess the impact of sequential removal of studies on all-cause mortality. CI: confidence interval; GUIDE-IT: Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure; HFrEF: heart failure with reduced ejection fraction; NT-proBNP: N-terminal pro–B-type natriuretic peptide; PRIMA: PRo-brain-natriuretic peptide guided therapy of chronic heart failure IMprove heart fAilure; RR: risk ratio; SIGNAL-HF: Swedish Intervention study–Guidelines and NT-proBNP AnaLysis in Heart Failure; TIME-CHF: Trial of Intensified versus Standard Medical Therapy in Elderly Patients With Congestive Heart Failure Randomized Trial.

NPs: Quantitative Marker of HF

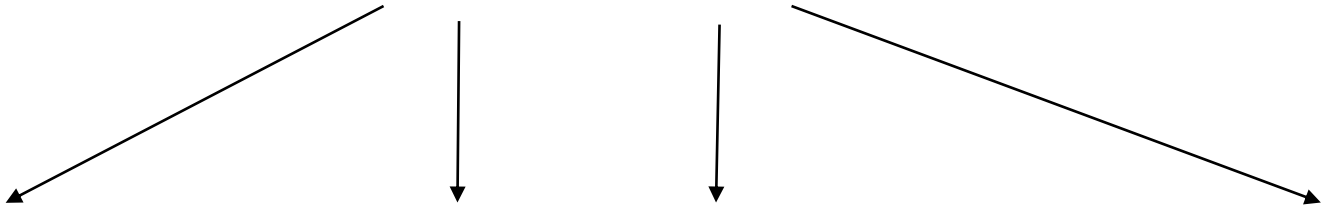


LV Syst. Dysfunction
+
LV Diast. Dysfunction
+
Valvular Dysfunction
+
RV Dysfunction

1) Diagnosis
2) Disease Severity

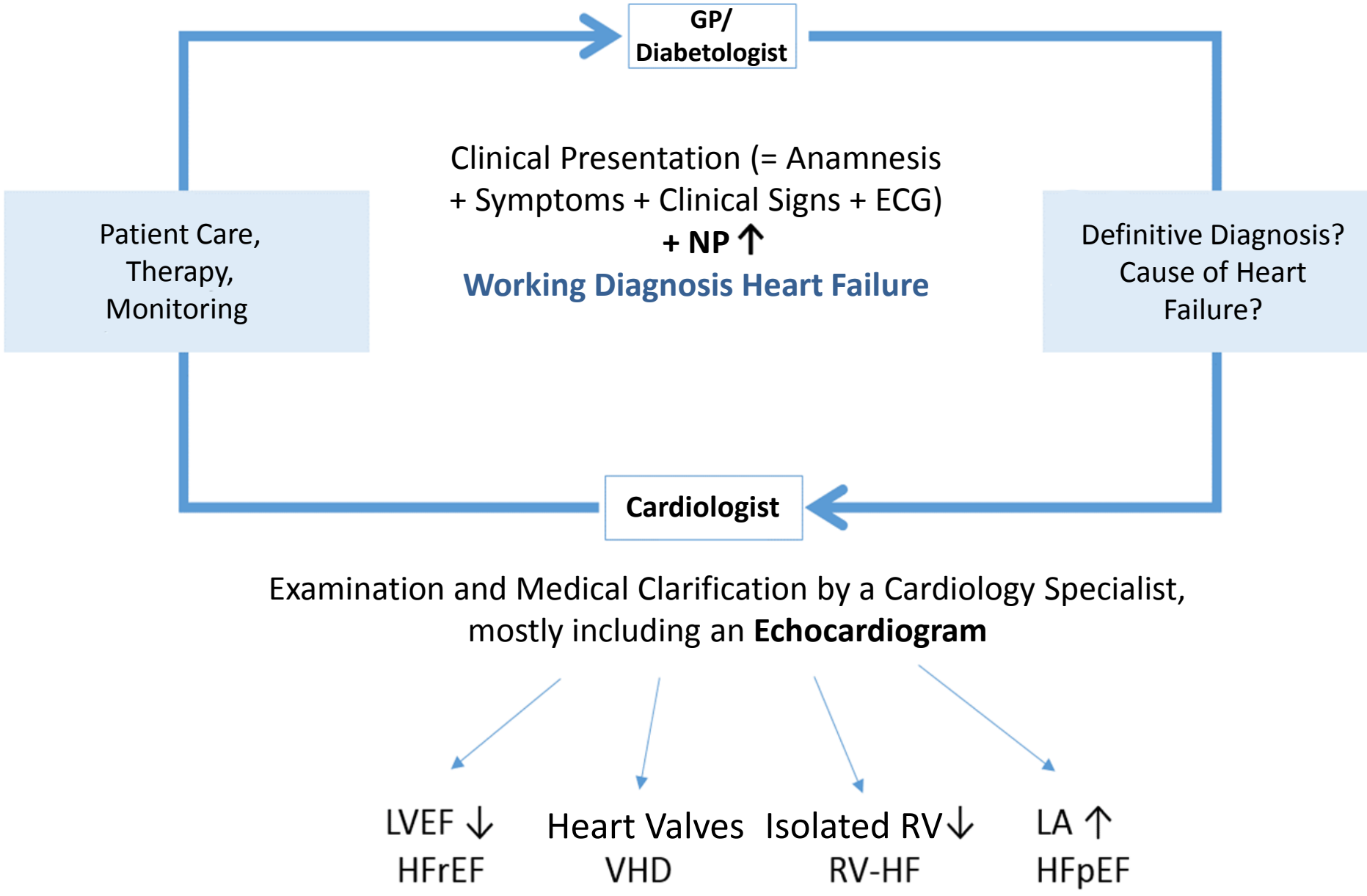
1) **HF-Diagnosis: Clinical** + ECG + chest x-ray + **NP**

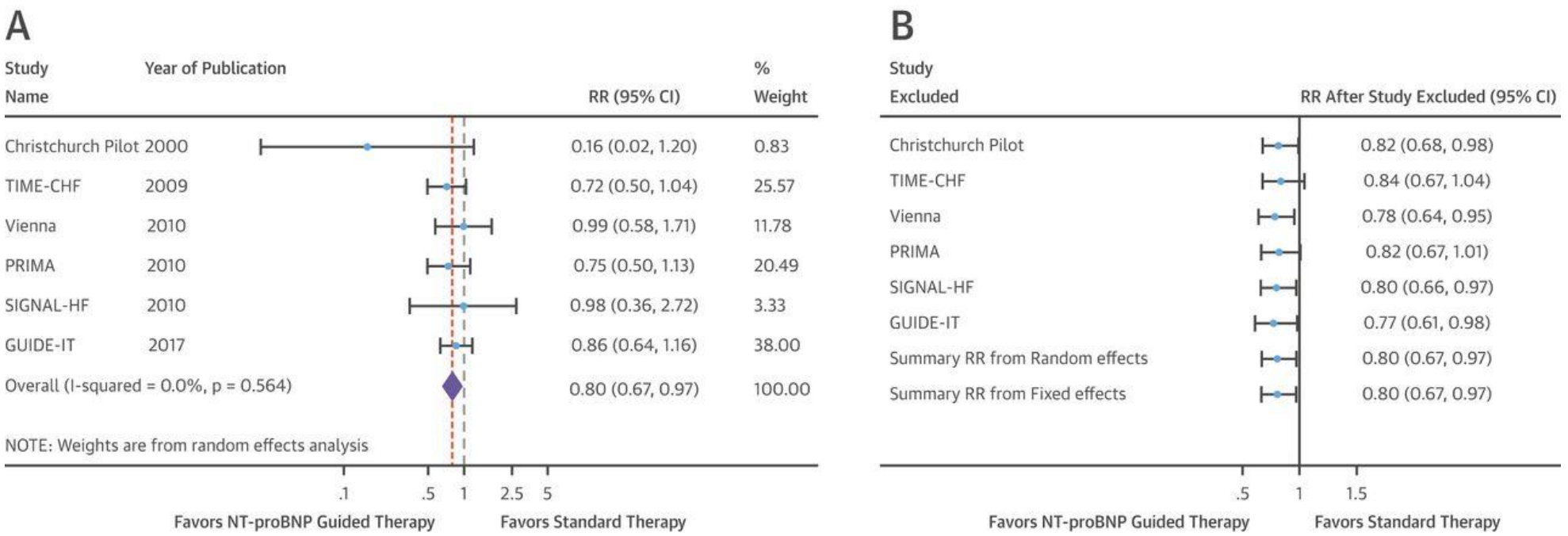
2) **HF-Phenotype:** **Echo**



LVEF ↓	Valves	isolated RV↓	**LA⇧**
HFrEF	VHD	RV-HF	**HFpEF**

HFmrEF
(LVEF 40-50%)


GP/
Diabetologist
Clinical Presentation (= Anamnesis
+ Symptoms + Clinical Signs + ECG)
+ NP ↑
Working Diagnosis Heart Failure
Patient Care,
Therapy,
Monitoring
Definitive Diagnosis?
Cause of Heart
Failure?
Cardiologist
Examination and Medical Clarification by a Cardiology Specialist,
mostly including an Echocardiogram
LVEF ↓
HFrEF
Heart Valves
VHD
Isolated RV ↓
RV-HF
LA ↑
HFpEF


A
Study Name
Year of Publication
RR (95% CI)
% Weight
Christchurch Pilot 2000 0.16 (0.02, 1.20) 0.83
TIME-CHF 2009 0.72 (0.50, 1.04) 25.57
Vienna 2010 0.99 (0.58, 1.71) 11.78
PRIMA 2010 0.75 (0.50, 1.13) 20.49
SIGNAL-HF 2010 0.98 (0.36, 2.72) 3.33
GUIDE-IT 2017 0.86 (0.64, 1.16) 38.00
Overall (I-squared = 0.0%, p = 0.564) 0.80 (0.67, 0.97) 100.00
NOTE: Weights are from random effects analysis
.1
.5
1
2.5
5
Favors NT-proBNP Guided Therapy
Favors Standard Therapy
B
Study Excluded
RR After Study Excluded (95% CI)
Christchurch Pilot 0.82 (0.68, 0.98)
TIME-CHF 0.84 (0.67, 1.04)
Vienna 0.78 (0.64, 0.95)
PRIMA 0.82 (0.67, 1.01)
SIGNAL-HF 0.80 (0.66, 0.97)
GUIDE-IT 0.77 (0.61, 0.98)
Summary RR from Random effects 0.80 (0.67, 0.97)
Summary RR from Fixed effects 0.80 (0.67, 0.97)
.5
1
1.5
Favors NT-proBNP Guided Therapy
Favors Standard Therapy